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| 10/086,082 | 02/28/2002 | Walter Brieden | A32213-PCT-USA-I | 3501 |

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| EXAMINER | |
|---|---|
| RAO, MANJUNATH N | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1652 | |

DATE MAILED: 11/25/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/086,082 | BRIEDEN ET AL. | |
| | Examin r | Art Unit | |
| | Manjunath N. Rao, Ph.D. | 1652 | |

*-- The MAILING DATE of this communication appears on the c ver sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *11 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *4-14,24 and 25* is/are pending in the application.

4a) Of the above claim(s) *4,5,24 and 25* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *6-14* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. §§ 119 and 120**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 09/214,679.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

## DETAILED ACTION

Claims 4-14, 24-25 are currently pending and are present for examination. Claims 6-14 are now under consideration. Claims 4-5, 24-25 remain withdrawn from consideration as being drawn to non-elected invention.

### *Election/Restrictions*

Applicant's election with traverse of Group II, Claims 6-12 in Paper filed on 9-11-03 is acknowledged. The traversal is on the ground(s) that coexamination of all of Groups I-III would not require independent searches and would not be undue burden on the Examiner. This is not found persuasive because while the searches for the three groups overlap, they are not coextensive. However, Examiner has now rejoined claims 13 and 14 drawn to microorganisms comprising a recombinant DNA molecule or a vector along with the elected group II. Claims drawn to Group I remain withdrawn from consideration. Applicants argue that the inventions of all three groups relate to polynucleotide and polypeptide and therefore would not be burdensome on the Examiner. Examiner respectfully disagrees. As explained in the previous Office action, the inventions of group I and Group II are distinct inventions. The search for Group I would each require the search of subclasses unnecessary for the search of elected Group II. Furthermore, the search involves extensive search of non-patent literature and protein and nucleic acid databases. Applicants also direct the Examiner's attention to the restriction requirement issued in the parent application (09/214,679) in which claims of the polypeptide and polynucleotide were placed in a single group. In response Examiner would like to point out

that the parent application was a 371 National Stage application and the lack-of-unity rules does not apply to US applications.

The requirement is still deemed proper and is therefore made FINAL.

Claims 4-5, 24-25 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention, the requirement having been traversed in Paper filed on 9-11-03.

***Priority***

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy has been filed in parent Application No. 09/214,679, filed on 12-30-99.

***Drawings***

Drawings submitted in this application are accepted by the Examiner for examination purposes only.

***Claim Objections***

Claim 7 is objected to because of the following informalities: Claim 7 recites the phrase "sequences...which are degenerated...". It appears that this is a typographical error and applicants meant to recite "degenerate". Appropriate correction is required.

Claims 6-7 and claims 8-14 all of which depend from claims 6 and 7 are objected to because of the following informalities: Claims 6-7 depend from non-elected claims. However,

in order to expedite the prosecution of the application, Examiner has incorporated the subject matter of claims 4 and 5 while examining above claims. Appropriate correction is required.

### *Claim Rejections - 35 USC § 101*

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 6-8 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. Claims 6-8 are drawn to "DNA sequence encoding.." which reads on a product of nature. Amending the claim to recite "An isolated polynucleotide encoding..." to show the hand of man would overcome the rejection.

### *Claim Rejections - 35 USC § 112*

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 7, 11 and claims 8-10, 12 which depend therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 6-7 and 11 recite the phrase "either of claims 4 and 5" and "either of claims 9 and 10" respectively. It is not clear to the Examiner as to whether applicants are claiming the dependency in the alternative or otherwise rendering the claims indefinite.

Claim 7 and claims 8-12 which depend therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 7 recites the phrase "which hybridize". However, the claim does not recite the specific hybridization conditions under which the polynucleotide has to hybridize rendering the claim indefinite. In view of the lack of specific hybridization conditions in the claim, Examiner has considered the claim broadly to include any hybridization condition (i.e., low stringency, medium stringency or high stringency). However, correction is required.

Claim 8 and claims 9-12 which depend therefrom are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claim 8 recites the phrase "characterized by the restriction map as shown in figure 1". It is highly unclear to the Examiner as to what characteristics applicants are referring to. It is not clear whether applicants are referring to the whole length of the nucleotide sequence or any nucleotide sequence comprising the same restriction sites in any order or any nucleotide sequence comprising any one or all the restriction sites etc. rendering the claim unclear. Furthermore, applicants need to provide a SEQ ID NO for the claimed sequence without which it would be impossible for the Examiner to do a search. Correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it

pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 10-14 are rejected because the invention appears to employ novel vectors/microorganisms. Applicants have described only a single vector, pPRS2a and a microorganism comprising said vector. However, the specification is silent regarding the vectors pPRS1b, pPRS4 and pPRS7 and the microorganisms comprising said vectors. Since all the vectors are essential to the claimed invention, they must be obtainable by a repeatable method set forth in the specification or otherwise be readily available to the public. The claimed plasmids' sequences are not fully disclosed, nor have all the sequences required for their construction been shown to be publicly known and freely available. The enablement requirements of 35 U.S.C. § 112 may be satisfied by a deposit of the plasmids. The specification does not disclose a repeatable process to obtain the vectors and it is not apparent if the DNA sequences are readily available to the public. Accordingly, it is deemed that a deposit of these plasmids should have been made in accordance with 37 CFR 1.801-1.809.

It is noted that applicants have deposited only the microorganism comprising the vector pPRS2a under the terms of Budapest Treaty but there is no indication in the specification as to public availability. As that specific vector has been deposited under the terms of the Budapest Treaty, an affidavit or declaration by applicants, or a statement by an attorney of record over his or her signature and registration number, stating that the specific strain (i.e., microorganism comprising pPRS2a) has been deposited under the Budapest Treaty and that the strain will be irrevocably and without restriction or condition released to the public upon the issuance of the patent, would satisfy the deposit requirement made herein.

Claims 6-9, 11-12 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a polynucleotide with SEQ ID NO:1 encoding an enzyme of SEQ ID NO:2 having amidohydrolase activity and capable of hydrolyzing R-3,3,3-trifluoro-2-hydroxy-2-methylpropionamide of Formula VI, does not reasonably provide enablement for any or all such polynucleotides from any source including those that are variants, mutants or functional equivalents or fragments of said polynucleotide or encoding a variant, mutant or functional equivalents or fragments of said polypeptide, or polynucleotides which simply hybridize to either SEQ ID NO:1 or fragments of the same under any hybridizing conditions. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 6-9, 11-12 are so broad as to encompass any polynucleotide encoding a polypeptide having amidohydrolase activity and capable of hydrolyzing R-3,3,3-trifluoro-2-hydroxy-2-methylpropionamide of Formula VI, from any source including those that are variants, mutants or functional equivalents or fragments of said polynucleotide or encoding a variant, mutant or functional equivalents or fragments (with or without activity) of said polypeptide, or polynucleotides which simply hybridize to either SEQ ID NO:1 or fragments of

the same under any hybridizing conditions. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polynucleotides broadly encompassed by the claims. Since polynucleotides encode amino acid sequence of a protein that determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence and obtain the desired activity requires a knowledge of and guidance with regard to which amino acids in the protein's sequence, (i.e., specific nucleotides in the polynucleotide) if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only a single amidohydrolase. It would require undue experimentation of the skilled artisan to make and use the claimed polynucleotides with an undefined function/activity. The specification is limited to teaching the use of SEQ ID NO: 1 for encoding SEQ ID NO:2 but provides no guidance with regard to the making of variants and mutants or fragments of the same or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polynucleotides, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in The Protein Folding Problem and Tertiary Structure Prediction, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to use the full scope of the polynucleotides encompassed by these claims.

While recombinant and mutagenesis techniques are known, it would be an undue burden to those skilled in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, and the positions within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompass all or any polynucleotide encoding a polypeptide with amidohydrolase activity including those that are variants, mutants or functional equivalents or fragments of said polynucleotide encoding a variant, mutant or functional equivalents or fragments of said polypeptide, or polynucleotides which simply hybridize to either SEQ ID NO:1 or fragments of the same under any hybridizing conditions because the specification does not establish: (A) regions of the polynucleotide encoding the protein structure which may be modified without affecting activity; (B) the general tolerance of amidohydrolase encoding polynucleotides to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any nucleotide (i.e., any amino acid residue) with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including polynucleotides with an enormous number of modifications in

the sequence. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of polynucleotides having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

Claims 6-9, 11-12 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. These claims are directed to a genus of DNA molecules lacking either the structure or the function or both.

The specification does not contain any disclosure of the structure of all DNA sequences that encode a polypeptide having amidohydrolase activity and capable of hydrolyzing R-3,3,3-trifluoro-2-hydroxy-2-methylpropionamide of Formula VI, including those that are variants, mutants or functional equivalents or fragments of said polynucleotide or functions of polynucleotides which simply hybridize to either SEQ ID NO:1 or fragments of the same under any hybridizing conditions. The genus of DNAs that comprise these above DNA molecules is a large variable genus with the potentiality of having many different functions (i.e., encoding many different proteins) or of having many different structure. Therefore, many structurally and functionally unrelated DNAs are encompassed within the scope of these claims, including partial DNA sequences. The specification discloses only a single species of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species

within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that the applicant had possession of the claimed invention at the time the instant application was filed. Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at www.uspto.gov.

***Conclusion***

None of the claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 703-306-5681. The examiner can normally be reached on 7.30 a.m. to 4.00 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy can be reached on 703-308-3804. The fax phone numbers for the organization where this application or proceeding is assigned are 703-308-4242 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-306-0196.

Manjunath N. Rao
November 19, 2003